Table 26 : Study DE019 : Erosion Score at Weeks 24 and Week 52 By Randomized Treatment Group – (full analysis set)

	Adalimumab					
	20 mg weekly		40 mg eow		Placebo	
Time point	N	Mean ± SD	N	Mean ± SD	N	Mean ± SD
Baseline	201	36.7 ± 31.4	194	41.4 ± 33.4	184	37.2 ± 25.8
Week 24						
Change at Week 24	189	0.3 ± 2.3	178	0.2 ± 2.9	166	0.7 ± 2.4
LOCF Week 24	193	0.3 ± 2.3	191	0.2 ± 2.8 [a]	179	0.7 ± 2.4
Week 52						
Change at Week 52	183	0.4 ± 2.6 [b]	165	0.0 ± 3.0 [b]	161	1.7 ± 4.6
LOCF Week 52	201	0.4 ± 2.5 [b]	194	0.0 ± 2.8 [b]	184	1.6 ± 4.4

[a] Statistically significantly different from placebo (p≤0.05).

[b] Statistically significantly different from placebo (p≤0.001).

Adalimumab-treated patients demonstrated less of an increase in JSN scores than placebo at Weeks 24 and 52 (Table 27). The nominal p-values for these comparisons were <0.005.

Table 27 : Study DE019 : Joint Space Narrowing: Change in Joint Space Narrowing and Joint Space Narrowing Scores at Weeks 24 and 52 by Randomized Treatment Group (full analysis set)

	Adalimumab					
	20 mg weekly		40 mg eow		Placebo	
Time point	N	Mean ± SD	N	Mean ± SD	N	Mean ± SD
Change in joint space narrowing score						
Baseline	201	29.7 ± 26.9	194	30.7 ± 29.2	184	29.2 ± 24.5
Week 24						
Change at Week 24	189	0.4 ± 2.9	178	0.1 ± 2.2	166	0.6 ± 2.0
LOCF change at Week 24	193	0.4 ± 2.9	191	0.1 ± 2.2	179	0.5 ± 2.0
Week 52						
Change at Week 52	183	0.5 ± 2.9	165	0.1 ± 2.4 [b]	161	1.1 ± 3.1
LOCF change at Week 52	201	0.5 ± 2.8	194	0.1 ± 2.3 [b]	184	1.0 ± 3.0
Patients with joint space narrowing scores (=0 and <0 versus >0) [c]						
Week 24						
Week 24	130	68.8 [a]	129	72.5 [b]	96	57.8
LOCF Week 24	132	68.4 [a]	138	72.3 [b]	103	57.5
Week 52						
Week 52	124	67.8 [b]	113	68.5 [b]	84	52.2
LOCF Week 52	138	68.7 [b]	135	69.6 [b]	100	54.3

[a] Statistically significantly different from placebo (p≤0.05).

[b] Statistically significantly different from placebo (p≤0.01).

[c] Comparison was done across two categories: (<0 and =0) and >0.

Table 28 presents the changes in TSS by quartiles and the 10^{th}/90^{th} percentiles. The 90^{th} percentile for changes in TSS was 3 units for adalimumab-treated patients compared to 10 units for placebo.

Table 28: Study DE019 : Change from baseline at Week 52 in TSS*

--Repeat Sponsor's primary analysis with additional quartiles of information

Group	n	mean	std	median	q1	q3	p10	p90	min	max
20 MG WEEKLY	196	0.79	4.94	0	-0.5	1.08	-2.0	3	-14.5	50.5
40 MG BIWEEKLY	183	0.09	4.77	0	-1.0	1.08	-2.5	3	-37.0	23.5
PLACEBO	172	2.67	6.76	1	0.0	4.00	-1.0	10	-25.0	39.0

*: Patients without baseline score or one score after baseline were excluded.
For patients without score at Week 52, their values were estimated using linear extrapolation method.

An analysis was performed to assess whether a linear imputation method or LOCF would be the best imputation technique for handling missing data. Table 29 demonstrates that similar results are seen for the 12-month change in TSS using the two imputation techniques. This is not surprising given the small amount of missing data in the trial.

Table 29 : Study DE019 : Comparison of Statistical Inference Conclusions Based on Change from Baseline at Week 52 in TSS* Using Different Imputation Methods

Imputation Method	40 MG BIWEEKLY (n=183)			PLACEBO (n=172)		
	Mean	SD	Median	Mean	SD	Median
Linear Extrapolation	0.09	4.77	0	2.67	6.76	1
LOCF	0.13	4.70	0	2.63	6.61	1

*: Patients without baseline score or one score after baseline were excluded.

Table 30 uses data for patients who had baseline, Week 24 and Week 52 x-ray assessments, and displays the difference between the actual Week-52 value and that obtained by imputing Week-52 values from Week-24 values using linear extrapolation or LOCF. For untreated patients, linear extrapolation closely approximated Week-52 values (mean difference = 0.05), while LOCF values differed markedly (mean difference = 1.48). This analysis suggests that linear extrapolation is a more accurate imputation technique.

Table 30 : Study DE019 : Difference Between the Real and the Imputed Values at Week 52 in TSS*

Imputation Method	40 MG BIWEEKLY (n=183)			PLACEBO (n=172)		
	Mean	SD	Median	Mean	SD	Median
Linear Extrapolation	-0.53	9.21	0	0.05	6.96	0
LOCF	-0.15	5.22	0	1.48	5.48	0.5

*: Patients without complete TSS score were excluded.

Table 31 presents additional sensitivity analyses to support the statistical findings of the primary analysis. Statistically significant differences between adalimumab and placebo remain when worse scores (75^{th} percentile) are imputed for missing values with adalimumab and better scores (25^{th} percentile) for placebo (Sensitivity Analysis III). A worse case scenario (Sensitivity Analysis IV) abrogates the treatment effect.

Table 31 : Study DE019 : Sensitivity Analyses Total Sharp Score

Sensitivity Analysis I
Assigning the worst change (50.5) to all patients with missing values

Group	n	mean	std	median	q1	q3	min	max	P-value*
20 MG WEEKLY	212	4.54	13.99	0.5	-0.5	2.00	-14.5	50.5	<0.0001
40 MG BIWEEKLY	207	5.93	16.79	0.0	-1.0	2.00	-37.0	50.5	<0.0001
PLACEBO	200	9.37	17.78	1.5	0.0	8.25	-25.0	50.5	

*: Adalimumab group vs. placebo group using Wilcoxon rank sum test.

Sensitivity Analysis II
Assigning the median change (0.5) to all patients with missing values

Group	n	mean	std	median	q1	q3	min	max	P-value*
20 MG WEEKLY	212	0.76	4.75	0.5	-0.5	1.00	-14.5	50.5	<0.0001
40 MG BIWEEKLY	207	0.13	4.48	0.0	-1.0	1.00	-37.0	23.5	<0.0001
PLACEBO	200	2.37	6.31	0.5	0.0	3.25	-25.0	39.0	

*: Adalimumab group vs. placebo group using Wilcoxon rank sum test.

Sensitivity Analysis III

Assigning the 75th percentile change (2.0) to patients with missing values treated with Adalimumab Assigning the 25th percentile change (-.5) to patients with missing values treated with placebo

Group	n	mean	std	median	q1	q3	min	max	P-value*
20 MG WEEKLY	212	0.88	4.76	0.5	-0.5	2.00	-14.5	50.5	0.051
40 MG BIWEEKLY	207	0.31	4.52	0.0	-1.0	2.00	-37.0	23.5	0.0054
PLACEBO	200	2.23	6.36	0.5	-0.5	3.25	-25.0	39.0	

*: Adalimumab group vs. placebo group using Wilcoxon rank sum test.

Sensitivity Analysis IV

Assigning the worst change (50.5) to patients with missing values treated with Adalimumab Assigning the best change (-37.0) to patients with missing values treated with placebo

Group	n	mean	std	median	q1	q3	min	max	P-value*
20 MG WEEKLY	212	4.54	13.99	0.5	-0.5	2.00	-14.5	50.5	0.8896
40 MG BIWEEKLY	207	5.93	16.79	0.0	-1.0	2.00	-37.0	50.5	0.9669
PLACEBO	200	-2.88	15.16	0.5	-0.5	3.25	-37.0	39.0	

*: Adalimumab group vs. placebo group using Wilcoxon rank sum test.

c. Disability Index of the HAQ at Week 52

An improvement in the disability index of the HAQ was represented by a negative mean change from baseline (i.e., assessed decrease in disease). After 52 weeks of treatment, both adalimumab dose groups (20 mg weekly and 40 mg q2w) were associated with statistically significant ($p = 0.001$) improvements in observed disability index (HAQ) compared to placebo (Table 32).

The change in disability index of the HAQ scores at Week 52 for the adalimumab treatment groups in the per-protocol set were also statistically significantly superior ($p<0.001$) to placebo. The scores at Week 52 were comparable between 20 mg weekly and 40 mg eow treatment groups

Normality was evaluated by applying the Shapiro-Wilk test procedure to the residuals from the parametric model. The resulting p-value was >0.05 indicating the normality assumption was not violated. The final analysis was therefore performed following a parametric approach. ANCOVA statistical analyses was utilized for change in modified change in disability index of the HAQ.

Table 32 : DE019 : Disability index of the HAQ at Week 52 by Randomized Treatment Group (full analysis set)

	Adalimumab				Placebo	
	20 mg weekly		40 mg eow			
Time point	N	Mean ± SD	N	Mean ± SD	N	Mean ± SD
Baseline	212	1.44 ± 0.64	206	1.45 ± 0.63	199	1.48 ± 0.59
Observed change at Week 52	168	-0.69 ± 0.55 [a]	160	-0.64 ± 0.57 [a]	140	-0.34 ± 0.54
LOCF change at endpoint	212	-0.61 ± 0.55 [a]	204	-0.59 ± 0.57 [a]	198	-0.25 ± 0.56

[a] Statistically significantly different from placebo (p≤0.001).

Among adalimumab-treated patients treated with 40 mg biweekly, 60% achieved HAQ (improvement) score reductions of ≥ 0.22 and 46% achieved HAQ score reductions of ≥ 0.50 units at 52 weeks. Among placebo-treated patients 41% achieved HAQ score reductions of ≥ 0.22 and 25% achieved HAQ score reductions of ≥ 0.50 units.

2. Secondary Efficacy Endpoints

A substantial number of adalimumab-treated patients demonstrated ACR50 responses (40%) at both Week 24 and Week 52 compared to placebo (10%) (Table 33). [Continuous secondary efficacy variables were to be analyzed using ANCOVA, with baseline and treatment group as covariates. Pearson's x^2 test was to be used for discrete data]

Table 33 : Study DE019 : ACR50 Response At Weeks 24 and 52: Number (%) of Patients Responding By Randomized Treatment Group

	Adalimumab		
Time point	**20 mg weekly** (N=212)	**40 mg q2w** (N=207)	**Placebo** (N=200)
Week 24	**87 (41) [a]**	**81 (39)[a]**	**19 (10)**
Week 52	**80 (38) [a]**	**86 (42) [a]**	**19 (10)**

[a] Statistically significantly different from placebo (p =0.001)

Over 20% of the 40 mg biweekly adalimumab-treated patients demonstrated ACR70 responses at both Week 24 and Week 52 (Table 34).

Table 34 : Study DE019 :ACR70 Response At Weeks 24 and 52: Numbers (%) of Patients Responding By Randomized Treatment Group

	Adalimumab		
	20 mg weekly	**40 mg q2w**	**Placebo**
Time point	(N=212)	(N=207)	(N=200)
Week 24	**37 (18) [a]**	**43 (21) [a]**	**5 (3)**
Week 52	**44 (21) [a]**	**48 (23) [a]**	**9 (5)**

[a] Statistically significantly different from placebo (p =0.001)
Source: sponsor's Table 30

A significantly greater proportion of adalimumab-treated patients than placebo experienced a major clinical response at Week 52, a unique achievement for a RA therapeutic agent in a 1-year study. (Table 35)

Table 35 : Study DE019 : Major Clinical Response at Week 52 by Treatment Group

	Adalimumab		
	20 mg weekly	40 mg q2w	Placebo
Major clinical response[a]	(N=212)	(N=207)	(N=200)
Yes	**20 (9.4)[b]**	**18 (8.7)[b]**	**3 (1.5)**

[a] Defined as a continuous ACR70 over a 6 month period

[b] Statistically significantly different from placebo (p =0.001)

The percentages of ACR50, ACR70 , and major clinical responses for adalimumab, all demonstrated statistical significance.

Table 36 demonstrates the higher number and percentage of placebo-treated patients compared to adalimumab-treated patients who were non-responders and required additional DMARDs.

Table 36 : Study DE019 : Number of Patients Using Additional DMARDs

Enrolled in study	N = 619			
Treatment	Adalimumab			
	20 mg Weekly N=212	40 mg Q2W N=207	All Adalimumab N=419	Placebo N=200
Completed study	168 (79%)	159 (77%)	327 (78%)	140 (70%)
Withdrew early	44 (21%)	48 (23%)	92 (22%)	60 (30%)
Number of patients using additional DMARDs				
Week 24				
ACR20 responder	0	2 (1%)	2 (1%)	1 (1%)
ACR20 non-responder	6 (3%)	7 (3%)	13 (3%)	31 (16%)
Week 52				
ACR20 responder	0	0	0	0
ACR20 non-responder	6 (3%)	8 (4%)	14 (3%)	30 (15%)

3. Summary of Efficacy Data

In this trial, there were three primary efficacy endpoints: the ACR20 response rate at Week 24 was the highest hierarchical primary efficacy outcome, followed by comparisons of the modified total Sharp x-ray score changes at Week 52, and the third primary efficacy endpoint was the disability index of the HAQ change at Week 52. The ACR20 response at Week 24 for both adalimumab-treatment groups (20 mg weekly [61%] and 40 mg q2w [63%], the proposed approval dosage) was statistically superior to the placebo-treated group (30%). The separation between adalimumab- and placebo-treated patients occurred as early as Week 2, was established by Week 4, and maintained through Week 52. All subsets of patients examined demonstrated a treatment effect of adalimumab.

Comparison of the change from baseline in modified total Sharp x-ray scores to Week 52 revealed a statistically significant difference between adalimumab-treatment groups and the placebo-treated group. The smaller changes observed in patients treated with adalimumab was consistent with a slowing of the rate of progressions of structural damage.

The study demonstrated a greater degree of improvement in the HAQ scores from baseline to Week 52 for both adalimumab doses compared to placebo. While these data are consistent with an important clinical benefit, they do not meet the criteria outlined in the guidance document for a claim of improvement in physical function/prevention of disability. Demonstration of sustained improvement for 2 years is required for this claim.

V. Study DE031 - Adalimumab Plus Stable Dose DMARD

A. Clinical Trial Design

Study DE031 is a multicenter, randomized, double-blind, placebo-controlled, phase III 24 week trial in which adalimumab 40 mg is self-administered subcutaneously (sc) every other week to patients with RA whose disease was not adequately treated with their current anti-rheumatic therapies. The primary objective is to contrast the safety profile of adalimumab with placebo when both are administered with pre-existing rheumatologic care in patients with active RA. The secondary objective is to determine and compare the efficacy of adalimumab with placebo when both are administered with pre-existing rheumatologic care. Efficacy is measured by ACR20 response criteria and improvement in physical function and health-related quality of life as measured by the HAQ and SF-36.

Patients had a confirmed diagnosis of RA (as defined by the 1987-revised ACR criteria) for at least 3 months and were in ACR functional class I, II, or III. Patients were inadequately treated with their current anti-rheumatic therapies and had active RA. Doses of DMARDs, as well as concomitant prednisone (≤ 10 mg daily) and NSAIDs, were required to be stable for at least 28 days prior to screening. At the baseline visit, patients were randomized to adalimumab or placebo (randomly assigned in a 1:1 ratio) and this signified the start of the 24-week placebo-controlled period. Patients were examined at Weeks 2, 4, 8, 12, 16, 20 and 24 of the study. Patients who failed to meet or maintain an ACR20 response were allowed a single increase in dosage of their DMARD and/or steroid therapy, treatment with another DMARD after 3 months of study participation, or further dose adjustments following consultation with the medical monitor. Patients who prematurely withdrew for lack of efficacy received usual medical care. All patients who completed the placebo-controlled period were eligible for enrollment into the open label continuation Study DE031X .

Planned enrollment for this study was 400 patients. However, based on changes made in Amendment B, the planned sample size was increased to 600 patients (Figure 11). Ultimately, 636 patients were analyzed, 318 in each treatment group, the adalimumab-treatment group and the placebo-treated group .

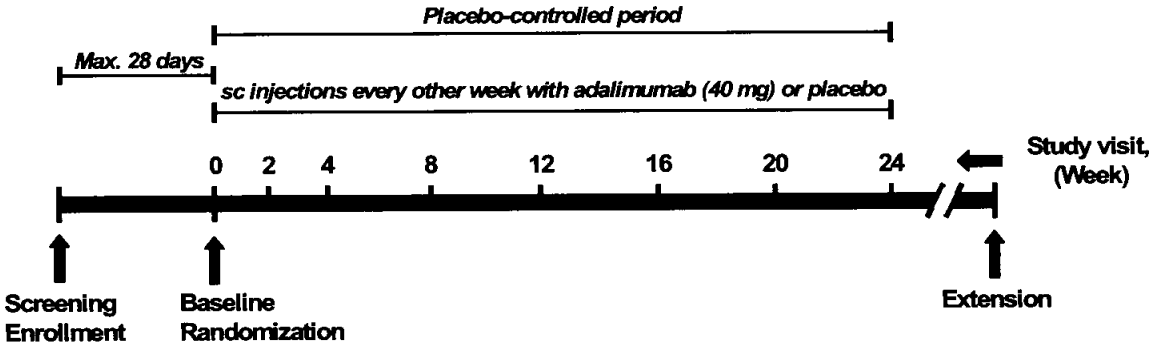

Figure 11: Study DE031 : Study Design

This study was designed to evaluate the safety and efficacy of adalimumab compared to a placebo control in patients with RA who were not adequately responding to other anti-rheumatic therapies and reflect the safety and efficacy that will be experienced post approval within usual current clinical practice. The study design reflected standard clinical practice, and therefore allowed adjunctive treatments and dose adjustments. A washout period for azathioprine and cyclosporine was chosen to decrease the potential for immunosuppression during the study.

Clinical adverse events (AEs), infections, immune reactions, malignancies, injection site reactions, changes in physical examinations, laboratory evaluations and vital signs were monitored. Chest x-rays and electrocardiograms (ECG) were done at study entry; an additional chest x-ray was performed at Week 12 in patients with positive tuberculin purified protein derivative (PPD) skin tests.

Eligibility consisted of RA patients with:
Inclusion criteria – major criteria for patients

- Patients were 18 years of age or older. Female patients of child-bearing potential had negative pregnancy test at screen.
- ACR criteria of active RA for at least 3 months (≥ 6 swollen joints and ≥9 tender joints)
- Receiving glucocorticoids equivalent to ≥10 mg of prednisone daily
- DMARD dose was required to remain unchanged for at least 28 days
- All males and females of reproductive potential used a reliable method of contraception.

Exclusion criteria – major criteria for patients

- Who had received previous treatment with total lymphoid irradiation, monoclonal antibodies, alkylating agents, any TNF antagonist, intravenous (iv) immunoglobulin or any investigational agent
- History of cancer, lymphoproliferative disease, or positive HIV status.
- History of or current acute inflammatory joint disease other than RA
- History of unstable, persistent, or chronic medical conditions, infection, active tuberculosis or listeriosis, iv antibiotics within 30 days, or oral antibiotics within 14 days prior to screening
- Pregnant or breast-feeding.
- History of clinically significant drug or alcohol abuse, drug abuse, having received intra-articular, intramuscular, or iv administration of corticosteroids within 4 weeks evaluation,
- Joint surgery within 2 months prior to the screening evaluation.
- Abnormal laboratory values: hematological, hepatic or renal

Concomitant therapy

All concomitant therapies, including over-the-counter preparations, taken by the patient during the study were recorded on the CRF. Patients were allowed to continue drug therapies including antirheumatic therapies during the study except for azathioprine and/or cyclosporine. Patients continued to receive their pre-study dose of anti-rheumatic therapies. Anti-rheumatic therapies permitted for use during the study included DMARDs (hydroxychloroquine, leflunomide, methotrexate, parenteral gold, oral gold and sulfasalazine, or any combination of these or other DMARDs), NSAIDs and oral or intra-articular steroids. Doses of these DMARDs as well as concomitant prednisone (=10 mg daily) and NSAIDs must have been stable for at least 28 days prior to screening. All efforts were made to keep the patient in the study during the 24-week placebo-controlled period.

Since this protocol was designed to reflect current clinical practice, the following adjunctive treatments and dose adjustments were allowed:

- Maximum of three intra-articular steroid injections were permitted during the first 3 months of the study (injected joint(s) were not assessed during joint examinations for 28 days following each injection).
- Dose of background DMARD, steroid, or NSAID therapies could be adjusted once during the study; further dose adjustments were instituted only after consultation with the medical monitor.

Secondary efficacy assessment - ACR20 response

The efficacy analysis was performed on the "full analysis set" of patients defined by the intent-to-treat principle. The full analysis set was defined as all patients who were randomized and received at least one injection of study drug and had at least one post-dose efficacy assessment. The ACR20 response at Week 24 (change from baseline) (using CRP as the acute phase reactant) was defined as the efficacy variable. All patients with missing visits or who withdrew from the study prematurely were counted as non-responders at the missing visits or from the time point of premature discontinuation onwards.

ACR20 response rates of the adalimumab and placebo-treated groups were compared using Pearson's $?^2$ test with a two-sided level of significance of a=0.05. All other efficacy variables were summarized descriptively (statistical characteristics, frequencies, percentages, confidence intervals) and analyzed by exploratory two-sided statistical tests. For categorical data, Pearson's $?^2$ test was used. For continuous data, an analysis of covariance (ANCOVA) model was used that included the treatment group as a factor and the respective baseline value as a covariate. In case of baseline imbalances between the treatment groups, further covariates could be added to the model.

A total of 400 patients were planned to be equally allocated to the two treatment groups, adalimumab 40 mg every other week and placebo. This sample size was chosen in order to increase the total number of patients exposed to adalimumab to approximately 300, thus allowing the study to be powered to show one adverse event with an incidence of 1% with at least 95% probability and with an incidence of 0.4% with at least 70% probability. Analysis of this enlarged safety database was intended for evaluation of any differences in AEs between patients treated with adalimumab *versus* standard rheumatologic care.

B. Study Conduct

Planned enrollment for this study was increased to 600 patients. Over 700 patients enrolled, 318 patients were randomized to each of the two treatment arms (adalimumab and placebo), and 91% of patients randomized to each treatment arm completed the study (Table 37). Dropouts occurred equally in both groups (9%). However, the number of dropouts due to lack of efficacy and/or progression of disease was higher in the placebo-treated group than in the adalimumab-treatment group. No increased incidence of withdrawals due to AEs was observed in the adalimumab-treatment group compared to the placebo-treated group.

A summary of patient disposition (all randomized patients) is presented in Figure 12 and Table 37. Due to the fact that one of the investigators (----------) was undergoing proceedings to be debarred, patients enrolled at his site (6 patients) were removed from the efficacy analysis. All randomized patients are included in the demographic and safety analyses.

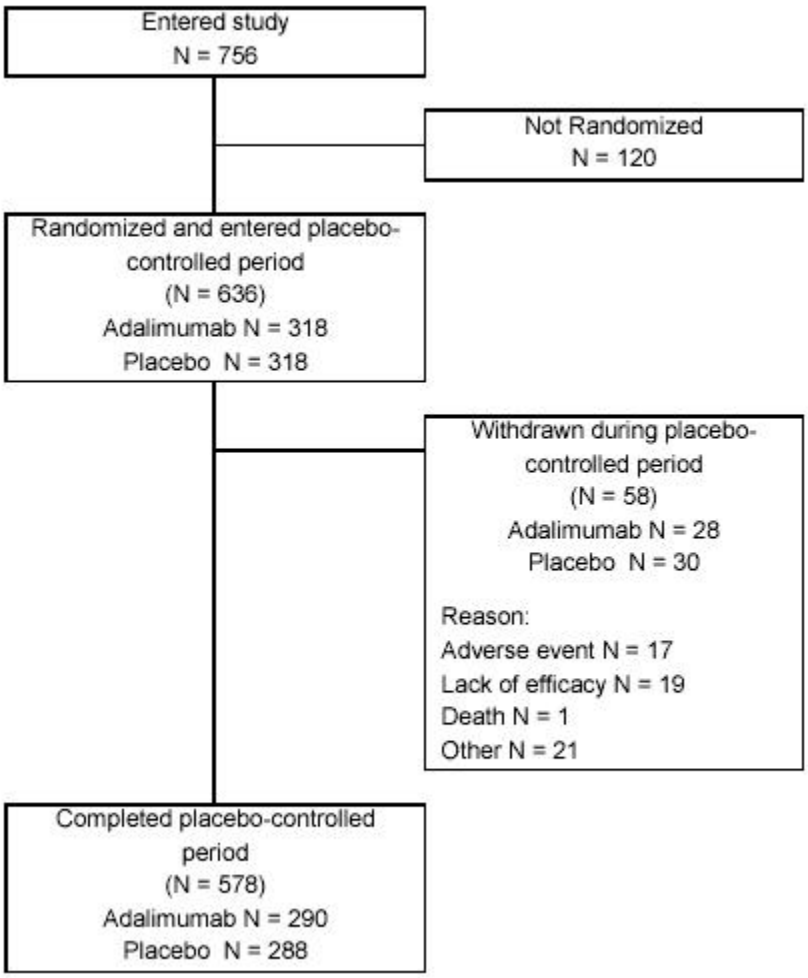

Figure 12 : StudyDE031 : Patient Disposition

Table 37 : Study DE031 : Patient Disposition (Number [%] of Patients) by Randomized Treatment Group (all randomized patients)

Result	Treatment group Adalimumab (N=318)	Placebo (N=318)	Total (N=636)
Completed study	290 (91)	288 (91)	578 (91)
Early discontinuation	28 (9)	30 (9)	58 (9)
Early withdrawals due to:			
Adverse event	9 (3)	8 (3)	17 (3)
Lost to follow-up	2 (1)	0 (0)	2 (0)
Protocol deviations	5 (2)	3 (1)	8 (1)
Death	1 (0)	0 (0)	1 (0)
Lack of efficacy and/or progression of disease	**5 (2)**	**14 (4)**	**19 (3)**
Administrative reasons	6 (2)	5 (2)	11 (2)

Table 38 : Study DE031 : Demographic characteristics at baseline by randomized treatment group (all randomized patients)

Demographic characteristic	Adalimumab (N=318)	Placebo (N=318)
Mean Age (years)	55	56
Female (%)	80	79
Ethnicity		
Caucasian (%)	89	86
Black (%)	4	6
Hispanic (%)	5	6
Mean Weight (kg)	78	76
Mean RA duration (years)	9	12
Rheumatoid Factor positive (%)	63	62
RA-relevant previous disease (at least one) (%)	56	59
Tender joint count (median)	25	25
Swollen joint count (median)	18	19
Patient global assessment of disease activity (mm on VAS)	53	52
Patient assessment of pain (mm on VAS)	57	58
Disability index (HAQ)	1.38	1.38
CRP (mg/dL) (mean)	1.5	1.5
FACIT Fatigue scale (median)	30	30
DMARD therapy		
DMARD discontinued prior (%)	56	56
Concomitant RA-specific DMARD therapy (%)	82	85
Concomitant RA-specific non-DMARD therapy (%)	99	96
Increase in DMARD dose (%)	2	4
Initiation of DMARD (%)	1	3
Increase in steroid dose (%)	4	6
Tuberculin PPD at baseline (N/%)		
PPD Positive	7/2	4/1
PPD Positive-on prophylaxis	4/1	3/1
PPD not stated-on prophylaxis	1/0	1/0

C. Safety Analysis

Comparable percentages of patients in the adalimumab and placebo treatment groups reported one or more treatment-emergent AEs during the study. The percentage of patients with AEs considered to be at least possibly related to study drug according to the investigator's assessment was higher in the adalimumab group than in the placebo group. Injection site reaction was significantly greater in patients receiving adalimumab than in patients receiving placebo. Neither the incidence of SAEs nor severe or life-threatening AEs was higher in the adalimumab-treated group. One death due to an AE was reported during the study. Patient #15106, treated with adalimumab, died following a SAE of herpes zoster, complicated by streptococcal superinfection (necrotizing fasciitis). No significant differences in the incidences of severe or life-threatening AEs, SAEs, or deaths were observed between the two treatment groups (Table 39). Summarization of all safety issues will be provide in the Integrated Safety Analysis.

Table 39 : Study DE031 : Overview of Patients with Treatment-Emergent AEs (safety set)

	Adalimumab (N = 318) (141.2 pt-yrs)		**Placebo (N = 318) (139.9 pt-yrs)**		**Adalimumab *vs.* Placebo**
Patients with any[a]	**N (%)**	**N/100 pt-yrs[b]**	**N (%)**	**N/100 pt-yrs[b]**	**p<0.05[c]**
AE	275 (87)	194.8	263 (83)	188.0	-
AE leading to death	1 (0)	0.7	0 (0)	0.0	-
SAE	17 (5)	12.0	22 (7)	15.7	-
AE resulting in withdrawal	9 (3)	6.4	7 (2)	5.0	-
AE resulting in dose interruption	38 (12)	26.9	27 (9)	19.3	-
Severe or life-threatening AE	38 (12)	26.9	49 (15)	35.0	-
At least possibly drug-related AE	147 (46)	104.1	111 (35)	79.3	Yes
Infection	166 (52)	117.6	157 (49)	112.2	-
Serious infection	4 (1)	2.8	6 (2)	4.3	-
Malignancy	4 (1)	2.8	0 (0)	0.0	Yes
Immunologic reaction	1 (0)	0.7	1 (0)	0.7	-
AE except injection site reaction	270 (85)	191.2	258 (81)	184.4	-
At least possibly drug-related AE except injection site reaction	117 (37)	82.9	89 (28)	63.6	Yes

[a] More than one AE per patient possible.
[b] Number of patients with AEs per 100 patient-years.
[c] Pearson's χ^2 test.

The numbers of patients reporting serious infections, malignancies, or immunologic reactions during this study were very small. The incidence of infections was similar for patients in the adalimumab and placebo treatment groups. A higher proportion of serious infections were reported in patients in the placebo-treated group (6 cases, 2%) compared to the adalimumab-treated group (4 cases, 1%). A higher proportion of patients in the adalimumab-treated group experienced malignancies (4 cases, 1%) compared to the placebo-treated patients (0 cases). The malignancies observed in the adalimumab-treated patients were 3 cases of basal cell carcinoma of the skin and one case of T-cell lymphoma. Patient 11601 was noted to have enlarged lymph nodes after three doses of study drug, was subsequently biopsied, and diagnosed with a T-cell lymphoma. The nominal p-value for the incidence of malignancies was <0.05. However, this does not take into account the multiple comparisons.

The mean duration and total number of injections of study drug were comparable in patients who received adalimumab or placebo. The mean total dose of adalimumab administered during the study was 481.4 mg.

A total of 9 (3%) of 318 adalimumab-treated patients and 7 (2%) of 318 placebo-treated patients withdrew from the study due to one or more treatment-emergent AEs. A summary of all patients who experienced AEs resulting in withdrawal is provided in Table 40. There were two cases of rashes and two cases of infections (infected foot and herpes zoster) among the adalimumab-treated patients leading to discontinuation from the study.

Table 40 : Study DE031 Patients Withdrawn Due to Treatment-Emergent AEs (safety set)

Pt. No.	Age, gender	Treatment	Adverse event (HARTS term)	Day on drug at onset	Duration (days)	Serious	Severity[a]	Relationship[b]	Outcome
3504	53, F	Adalimumab	Rash	104	--	No	Grade 1	Possible	Not resolved
10311	65, F	Placebo	Congestive heart failure	34	9	Yes	Grade 2	Unrelated	Resolved
10410	68, F	Adalimumab	Rash	16	9	No	Grade 1	Possible	Resolved
11601	64, M	Adalimumab	Neoplasm	58	--	Yes	Grade 3	Unlikely	Not resolved
11613	61, M	Adalimumab	Infection[c]	82	45	Yes	Grade 2	Unrelated	Resolved
11614	62, M	Placebo	Pneumonia	93	5	Yes	Grade 2	Possible	Resolved
12102	55, F	Adalimumab	Laboratory test abnormal	1	--	No	Grade 1	Unrelated	Not resolved
12115	70, F	Adalimumab	Hypertensive encephalopathy	15	7	Yes	Grade 3	Possible	Resolved
13203	61, F	Placebo	Abdominal pain	29	45	No	Grade 3	Possible	Resolved
13309	36, M	Adalimumab	Bursitis	53	--	No	Grade 3	Unlikely	Not resolved
13403	63, F	Adalimumab	Laboratory test abnormal	140	--	Yes	Grade 2	Probable	Not resolved
13601	52, F	Placebo	Dyspnea	57	1	No	Grade 3	Unlikely	Resolved
15006	58, F	Placebo	Abscess	73	--	Yes	Grade 3	Unrelated	Resolving
15106[d]	70, M	Adalimumab	Herpes zoster	7	--	No[d]	Grade 2	Possible	Not resolved
15712	52, F	Placebo	Cellulitis	85	--	No	Grade 2	Possible	Not resolved
15901	71, F	Placebo	Pneumonia	31	74	No	Grade 2	Possible	Resolved

[a] Grade 1 = mild; Grade 2 = moderate; Grade 3 = severe; Grade 4 = life-threatening.

[b] Relationship to study drug as determined by the investigator.

[c] Infection of right foot.

[d] At the time of withdrawal, the herpes zoster AE in Patient #15106 was not an SAE. Entries in this table reflect the status at the time of study withdrawal. The patient ultimately died due to this AE (see Section 5.3.2).

F: female; M: male

Comparison of the AEs subsetted by concomitant DMARD subgroups is summarized in Table 41. A higher rate of certain categories of associated AEs with certain concomitant DMARDs was seen. AEs resulted in a higher incidence of dose interruption when leflunomide was combined with adalimumab (8 cases, 19%) compared to placebo (1 case, 2%). In addition, AEs at least possibly adalimumab-related were more frequent when adalimumab was given concomitantly with MTX, leflunomide, and other DMARDs, but not with antimalarials and sulfasalazine. A higher rate of SAEs was seen among placebo-treated patients than adalimumab-treated patients when given concomitantly with MTX and antimalarials.

Comparison of the number (percentage) of patients with the most frequently reported treatment-related AEs subsetted by number of concomitant DMARDs, shows a higher incidence of AEs that were considered drug-related when adalimumab is given alone or with one additional DMARD compared to placebo. There was no clear pattern of an increase in AEs overall among patients receiving adalimumab along with two or three additional DMARDs (Table 42).

Comparison of the number (percentage) of patients with the most frequently reported treatment-related AEs by concomitant DMARD therapy does not demonstrate a higher frequency of adalimumab-related AEs (Table 43). Comparison of the number (percentage) of patients with the most frequently reported treatment-related AEs corrected for frequency per 100 patient years reveals that rash, injection site reaction, and back pain were seen more frequently among adalimumab-treated patients \than placebo-treated patients with a nominal p value of < 0.05.

Table 41 : Study DE031 : Overview of Treatment-Emergent AEs by Concomitant DMARD Therapy [a] (safety set)

	Methotrexate		Antimalarials		Leflunomide		Sulfasalazine		Other DMARDs	
	Adalimumab	Placebo	Adalimumab	Placebo	Adalimumab	Placebo	Adalimumab	Placebo	Adalimumab	Placebo
Patients with any[a]	(N=178) N (%)	(N=199) N (%)	(N=75) N (%)	(N=82) N (%)	(N=42) N (%)	(N=46) N (%)	(N=29) N (%)	(N=33) N (%)	(N=25) N (%)	(N=25) N (%)
Adverse Event	153 (86)	161 (81)	63 (84)	74 (90)	39 (93)	39 (85)	23 (80)	28 (85)	23 (92)	19 (76)
AE leading to death	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
SAE	8 (5)	17 (9)	4 (5)	7 (9)	3 (7)	2 (4)	2 (7)	1 (3)	0 (0)	0 (0)
AE resulting in withdrawal	5 (3)	4 (2)	0 (0)	2 (2)	2 (5)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)
AE resulting in dose interruption	16 (9)	13 (7)	7 (9)	6 (7)	8 (19)	1 (2)	2 (7)	4 (12)	1 (4)	3 (12)
Severe or life-threatening AE	19 (11)	28 (14)	7 (9)	13 (16)	8 (19)	8 (17)	5 (17)	5 (15)	1 (4)	2 (8)
At least possibly drug-related AE	78 (44)	67 (34)	37 (49)	40 (49)	23 (55)	18 (39)	14 (48)	14 (42)	14 (56)	9 (36)
Infection	100 (56)	96 (48)	34 (45)	48 (59)	24 (57)	21 (46)	13 (45)	15 (46)	14 (56)	15 (60)
Serious infection	4 (2)	4 (2)	1 (1)	3 (4)	0 (0)	2 (4)	1 (3)	0 (0)	0 (0)	0 (0)
Malignancy	2 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Immunologic reaction	0 (0)	1 (1)	0 (0)	1 (1)	0 (0)	0 (0)	1 (3)	0 (0)	0 (0)	0 (0)

[a] .More than one AE per patient possible.

Table 42 : Study DE031 : Overview of Treatment-Emergent AEs by Number of Concomitant DMARD Therapies (safety set)

Number of concomitant DMARDs	0		1		2		3	
	Adalimumab	Placebo	Adalimumab	Placebo	Adalimumab	Placebo	Adalimumab	Placebo
Patients with any[a]	(N=57) N (%)	(N=48) N (%)	(N=184) N (%)	(N=172) N (%)	(N=66) N (%)	(N=84) N (%)	(N=11) N (%)	(N=14) N (%)
AE	46 (81)	36 (75)	166 (90)	145 (84)	54 (82)	72 (86)	9 (82)	10 (71)
AE leading to death	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
SAE	3 (5)	2 (4)	12 (7)	13 (8)	1 (2)	7 (8)	1 (9)	0 (0)
AE resulting in withdrawal	2 (4)	1 (2)	7 (4)	5 (3)	0 (0)	1 (1)	0 (0)	0 (0)
AE resulting in dose interruption	10 (18)	4 (8)	22 (12)	19 (11)	6 (9)	4 (5)	0 (0)	0 (0)
Severe or life-threatening AE	7 (12)	7 (15)	23 (13)	30 (17)	7 (11)	10 (12)	1 (9)	2 (14)
At least possibly drug-related AE	**22 (39)**	**11 (23)**	**90 (49)**	**60 (35)**	**29 (44)**	**33 (39)**	**6 (55)**	**7 (50)**
Infection	28 (49)	17 (35)	99 (54)	93 (54)	31 (47)	41 (49)	8 (73)	6 (43)
Serious infection	0 (0)	0 (0)	3 (2)	3 (2)	0 (0)	3 (4)	1 (9)	0 (0)
Malignancy	2 (4)	0 (0)	2 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Immunologic reaction	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)

[a] More than one AE per patient possible.

Table 43: Study DE031: Number (%) of Patients with The Most Frequently Reported Treatment-Emergent AEs by Concomitant DMARD Therapy (safety set)

AEs[c]	Methotrexate		Antimalarials		Leflunomide		Sulfasalazine		Other	
	Adalimumab (N=178) N (%)	Placebo (N=199) N (%)	Adalimumab (N=75) N (%)	Placebo (N=82) N (%)	Adalimumab (N=42) N (%)	Placebo (N=46) N (%)	Adalimumab (N=29) N (%)	Placebo (N=33) N (%)	Adalimumab (N=25) N (%)	Placebo (N=25) N (%)
Upper respiratory infection	32 (18)	28 (14)	16 (21)	18 (22)	7 (17)	8 (17)	6 (21)	5 (15)	9 (36)	5 (20)
Injection site pain	20 (11)	22 (11)	10 (13)	12 (15)	6 (14)	7 (15)	2 (7)	2 (6)	3 (12)	1 (4)
Rash	16 (9)	8 (4)	3 (4)	4 (5)	5 (12)	3 (7)	3 (10)	2 (6)	2 (8)	3 (12)
Injection site reaction	13 (7)	2 (1)	8 (11)	2 (24)	4 (10)	0 (0)	3 (10)	1 (3)	2 (8)	0 (0)
Nausea	16 (9)	11 (6)	10 (13)	4 (5)	6 (14)	3 (7)	3 (10)	2 (6)	1 (4)	0 (0)
Urinary tract infection	21 (12)	10 (5)	6 (8)	7 (9)	5 (12)	1 (2)	0 (0)	2 (6)	1 (4)	2 (8)
Headache	13 (7)	13 (7)	12 (16)	9 (11)	3 (7)	2 (4)	3 (10)	3 (9)	0 (0)	1 (4)
Sinusitis	16 (9)	13 (7)	9 (12)	9 (11)	2(5)	2 (4)	0 (0)	2 (6)	0 (0)	4 (16)
Flu syndrome	13 (7)	7 (4)	5 (7)	3 (4)	2 (5)	2 (4)	2 (7)	1 (3)	2 (8)	3 (12)
Accidental injury	16 (9)	11 (6)	6 (8)	9 (11)	3 (7)	4 (9)	3 (10)	3 (9)	1 (4)	2 (8)
Abdominal pain	9 (5)	9 (5)	2 (3)	5 (6)	2 (5)	1 (2)	3 (10)	1 (3)	0 (0)	0 (0)
Rhinitis	17 (10)	24 (12)	5 (7)	9 (11)	2 (5)	6 (13)	3 (10)	3 (9)	2 (8)	1 (4)
Diarrhea	14 (8)	12 (6)	6 (8)	7 (9)	3 (7)	7 (15)	1 (3)	2 (6)	1 (4)	0 (0)
Clinical flare reaction	8 (5)	10 (5)	3 (4)	5 (6)	3 (7)	3 (7)	4 (14)	2 (6)	1 (4)	2 (8)
Back pain	11 (6)	3 (2)	2 (3)	1 (1)	4 (10)	1 (2)	3 (10)	2 (6)	4 (16)	0 (0)
Surgery	8 (5)	6 (3)	5 (7)	3 (4)	3 (7)	0 (0)	0 (0)	1 (3)	1 (4)	0 (0)

[a] Occurring in ≥5% of patients in any treatment group.
[b] MTX = methotrexate; Antimal = antimalarials (eg, HCG, chloroquine); Leflu = leflunomide; Sulfasal = sulfasalazine; Other = other DMARDs.
[c] More than one AE per patient possible.

Table 44 lists all the patients in Trial DE031 with SAEs. Eighteen occurred among adalimumab-treated patients and 22 occurred among placebo-treated patients. There was no clear pattern of SAEs among adalimumab-treated patients.

Table 44 : Study DE031 : Patients with SAEs (safety set)

Treatment/ Pt. No.	Age, gender	Adverse event (HARTS term)	Day on drug at onset	Duration (days)	Severity[a]	Relationship[b]
Adalimumab						
13403	63, F	Laboratory test abnormal	140	-	Grade 2	Probable
12115	70, F	Hypertensive encephalopathy	15	7	Grade 3	Possible
15106	70, M	Skin disorder, Herpes zoster[c]	12	16	Grade 3, 4[c]	Possible
9708	67, F	Asthma	91	43	Grade 2	Unlikely
10203	81, M	Gastrointestinal hemorrhage	152	4	Grade 2	Unlikely
11601	64, M	Neoplasm [T-cell lymphoma]	58	-	Grade 3	Unlikely
12603	23, M	Gastrointestinal disorder	4	2	Grade 3	Unlikely
13502	75, F	Congestive heart failure	13	3	Grade 2	Unlikely
2706	45, F	Bone fracture [not spontaneous]	38	76	Grade 3	Unrelated
10506	52, F	Skin carcinoma [basal cell carcinoma]	15	21	Grade 2	Unrelated
11110	61, F	Chest pain	-16	3	Grade 3	Unrelated
11613	61, M	Infection	82	45	Grade 2	Unrelated
11703	69, M	Myocardial infarction	95	4	Grade 4	Unrelated
11914	44, F	Tachycardia, arrhythmia	173	6	Grade 3	Unrelated
12001	43, F	Gastrointestinal disorder	35	5	Grade 3	Unrelated
12112	74, F	Surgery	65	11	Grade 2	Unrelated
12905	46, F	Pelvic pain	22	34	Grade 3	Unrelated
15713	58, M	Kidney calculus	86	7	Grade 3	Unrelated
Placebo						
15714	44, F	Pneumonia	85	10	Grade 3	Possible
16006	46, F	Gastrointestinal disorder [torsion of appendiceal fat]	22	8	Grade 3	Possible
13601	52, F	Asthma	57	2	Grade 4	Possible
10712	72, F	Bronchitis	164	4	Grade 3	Possible
11614	62, M	Pneumonia	93	5	Grade 2	Possible
10708	78, F	Bronchitis	6	5	Grade 2	Unlikely
10711	66, F	Colitis	117	4	Grade 3	Unlikely
11604	69, F	Thrombosis leg	170	8	Grade 2	Unlikely
11607	58, F	Lung disorder, abdominal pain	51	4	Grade 2	Unlikely
11611	74, F	Atrial fibrillation	95	4	Grade 3	Unlikely
15107	60, F	Chest pain	99	2	Grade 3	Unlikely
10311	65, F	Congestive heart failure	34	9	Grade 2	Unrelated
11106	57, F	Myocardial infarction	48	4	Grade 3	Unrelated
11114	46, F	Vaginal hemorrhage	4	3	Grade 3	Unrelated
11616	56, F	Pulmonary embolus	70	8	Grade 3	Unrelated
12502	59, M	Surgery	84	4	Grade 2	Unrelated
13103	53, M	Neck pain	170	2	Grade 3	Unrelated
13408	42, F	Psychosis	148	3	Grade 3	Unrelated
13602	55, F	Cardiomyopathy	141	5	Grade 3	Unrelated
14903	35, F	Anaphylactic reaction	79	1	Grade 2	Unrelated
15006	58, F	Abscess	73	-	Grade 3	Unrelated
15305	68, F	Adenoma	84	7	Grade 3	Unrelated

[a] Grade 1 = mild; Grade 2 = moderate; Grade 3 = severe; Grade 4 = life-threatening.

[b] Relationship to study drug as determined by the investigator.

[c] Herpes zoster infection began as a skin disorder of moderate severity and progressed to streptococcal superinfection (necrotizing fasciitis) and sepsis.

F: female; M: male

One adalimumab-treated patient (Patient #15106) died during the study (Table 45). This patient developed herpes zoster 12 days after the first injection of adalimumab, which then progressed into a streptococcal group A superinfection at the site of the herpes lesions. This progressed to necrotizing fasciitis and sepsis. The patient was admitted to the hospital and underwent surgical debridement of the lesion. The patient never recovered and died 16 days after the appearance of the herpetic lesions. This adalimumab-treated patient was also taking prednisone and methotrexate for control of RA.

Table 45 : Study DE031 Patient with fatal AE (safety set)

Patient number	Age Gender	Treatment	Adverse event (HARTS term)	Day on drug at onset	Duration (days)	Severity	Relationship[a]
			Skin disorder				
15106	**70 Male**	**Adalimumab**	**Herpes zoster[b]**	**12**	**16**	**Grade 3, 4[b]**	**Possible**

[a] Relationship to study drug as determined by the investigator.
[b] Herpes zoster infection began as a skin disorder of moderate severity and progressed to streptococcal superinfection (necrotizing fasciitis) and sepsis.

Serious infectious AEs were reported in ten study patients, 4 (1.3% of 318) adalimumab-treated patients and 6 (1.9% of 318) placebo-treated patients (Table 46). Among the adalimumab-treated patients, there were 2 cases of gastrointestinal disorder (appendicitis), 1 case of herpes zoster, and 1 case of foot infection. Approximately 50% of both adalimumab-treated and placebo-treated patients reported one or more non-serious infectious AEs after study drug administration.

Table 46 : Study DE031 : Patients with serious infections (safety set)

Pt. No.	Age, gender	Treatment	Adverse event (HARTS term)	Day on drug at onset	Duration (days)	Severity[a]	Relation-ship[b]	Outcome
10708	78, F	Placebo	Bronchitis	6	5	Grade 2	Unlikely	Resolved
10711	66, F	Placebo	Colitis[c]	117	4	Grade 3	Unlikely	Resolved
10712	72, F	Placebo	Bronchitis	164	4	Grade 3	Possible	Resolved
11613	61, M	Adalimumab	Infection[d]	82	45	Grade 2	Unrelated	Resolved
11614	62, M	Placebo	Pneumonia	93	5	Grade 2	Possible	Resolved
12001	43, F	Adalimumab	Gastrointestinal disorder[e]	35	5	Grade 3	Unrelated	Resolved
12603	23, M	Adalimumab	Gastrointestinal disorder[e]	4	2	Grade 3	Unlikely	Resolved
15006	58, F	Placebo	Abscess	73	--	Grade 3	Unrelated	Resolving
15106	70, M	Adalimumab	Skin disorder, Herpes zoster	12	16	Grade 3, 4	Possible	Fatal
15714	44, F	Placebo	Pneumonia	85	10	Grade 3	Possible	Resolved

[a] Grade 1 = mild; Grade 2 = moderate; Grade 3 = severe; Grade 4 = life-threatening.

[b] Relationship to study drug as determined by the investigator.

[c] Clostrium difficile.

[d] Infection of right foot.

[e] Appendicitis.

[f] Herpes zoster infection began as a skin disorder of moderate severity and progressed to streptococcal superinfection (necrotizing fasciitis) and sepsis.

F: female; M: male

The six most frequently reported infectious AEs (upper respiratory infection, rhinitis, sinusitis, urinary tract infection, flu syndrome, and cough increased) are presented by concomitant DMARDs subgroups (with and without methotrexate, antimalarials, leflunomide, sulfasalazine, or other DMARDs) in Table 47 and summarized by the number of concomitant DMARDs in Table 48. There was no clear pattern of an increase in any particular type of infection beyond the fluctuations expected when large numbers of comparisons are considered.

Although there were individual subgroups where the incidence of particular infections was somewhat higher in adalimumab-treated patients than in controls, there was no overall pattern of more frequent infections associated with concomitant use of higher numbers of DMARDs (Table 48).

Table 47: Study DE031 Frequent infectious adverse events by concomitant DMARD therapy (safety set)

	Methotrexate		Antimalarials		Leflunomide		Sulfasalazine		Other DMARDs	
	Adalimumab (N=178)	Placebo (N=199)	Adalimumab (N=75)	Placebo (N=82)	Adalimumab (N=42)	Placebo (N=46) N	Adalimumab (N=29)	Placebo (N=33)	Adalimumab (N=25)	Placebo (N=25)
AEs	N (%)	N (%)	N (%)	N (%)	N (%)	(%)	N (%)	N (%)	N (%)	N (%)
Upper respiratory infection	32 (18.0)	28 (14.1)	16 (21.3)	18 (22.0)	7 (16.7)	8 (17.4)	6 (20.7)	5 (15.2)	9 (36.0)	5 (20.0)
Rhinitis	17 (9.6)	24 (12.1)	4 (5.3)	9 (11.0)	2 (4.8)	6 (13.0)	2 (6.9)	3 (9.1)	2 (8.0)	1 (4.0)
Sinusitis	16 (9.0)	13 (6.5)	9 (12.0)	9 (11.0)	2 (4.8)	2 (4.3)	0 (0.0)	2 (6.1)	0 (0.0)	4 (16.0)
Urinary tract infection	21 (11.8)	10 (5.0)	6 (8.0)	7 (8.5)	5 (11.9)	1 (2.2)	0 (0.0)	2 (6.1)	1 (4.0)	2 (8.0)
Flu syndrome	13 (7.3)	7 (3.5)	5 (6.7)	3 (3.7)	2 (4.8)	2 (4.3)	2 (6.9)	1 (3.0)	2 (8.0)	3 (12.0)
Cough increased	6 (3.4)	8 (4.0)	2 (2.7)	1 (1.2)	0 (0.0)	1 (2.2)	2 (6.9)	1 (3.0)	0 (0.0)	2 (8.0)

Table 48: Study DE031:Frequency of the most commonly reported infectious adverse events by number of concomitant DMARD therapies (safety set)

Number of concomitant DMARDs	0		1		2		≥3	
	Adalimumab (N=57)	Placebo (N=48)	Adalimumab (N=184)	Placebo (N=172)	Adalimumab (N=66)	Placebo (N=84)	Adalimumab (N=11)	Placebo (N=14)
AEs	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Upper respiratory infection	11 (19.3)	9 (18.8)	38 (20.7)	19 (11.0)	10 (15.2)	16 (19.0)	4 (36.4)	4 (28.6)
Rhinitis	3 (5.3)	2 (4.2)	10 (5.4)	21 (12.2)	7 (10.6)	9 (10.7)	1 (9.1)	1 (7.1)
Sinusitis	4 (7.0)	3 (6.3)	14 (7.6)	21 (12.2)	5 (7.6)	3 (3.6)	1 (9.1)	1 (7.1)
Urinary tract infection	2 (3.5)	2 (4.2)	21 (11.4)	10 (5.8)	6 (9.1)	6 (7.1)	0 (0.0)	0 (0.0)
Flu syndrome	6 (10.5)	3 (6.3)	10 (5.4)	10 (5.8)	7 (10.6)	3 (3.6)	0 (0.0)	0 (0.0)
Cough increased	8 (14.0)	1 (2.1)	5 (2.7)	9 (5.2)	1 (1.5)	2 (2.4)	1 (9.1)	0 (0.0)

Similar numbers of adalimumab-treated patients and placebo-treated patients withdrew from the study due to one or more treatment-emergent AEs.

A higher percentage of adalimumab-treated patients converted from negative to positive ANA than placebo-treated patients during this trial. The percentage was notably higher at Week 24 than at Week 12 (Table 49).

Table 49 : Study DE031 : Patients who changed from positive to negative or negative to positive ANA until Week 12 or Week 24 [a] (safety set)

ANA titer change	Treatment	
	Adalimumab (N=318)	Placebo (N=318)
Baseline negative, Week 12 positive	31	24
Baseline positive, Week 12 negative	14	10
Baseline negative, Week 24 positive	66	39
Baseline positive, Week 24 negative	6	5

[a] Positive titer is ≥1:80.

Likewise, a higher percentage of adalimumab-treated patients converted from negative to positive anti-dsDNA than placebo-treated patients during this trial. The percentage was much higher at Week 24 (Table 50). One patient with rising ANA and anti-dsDNA titers was discontinued from the study. No clinical manifestations of lupus-like syndrome were observed among patients who became positive for autoantibodies.

Table 50: Study DE031 : Patients who changed from positive to negative or negative to positive anti-dsDNA until Week 12 or Week 24 [a] (safety set)

Anti-dsDNA titer change	Treatment	
	Adalimumab (N=318)	Placebo (N=318)
Baseline negative, Week 12 positive	2	0
Baseline positive, Week 12 negative	0	0
Baseline negative, Week 24 positive	36	3
Baseline positive, Week 24 negative	3	0

[a] Positive values are >3.5 IU/mL.